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PATENT
Docket MZ 100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of : MICHAEL A. ZASLOFF

Serial No. 10/053,299 Examiner: Sheikh, Humera N.
Filed: 01/17/2002 Art Unit 1615
Title: METHODS AND COMPOSITIONS FOR BLOCKING MICROBIAL ADHERENCE TO EUKARYOTIC CELLS

CERTIFICATE OF MAILING

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Signature of certifier

Henry E. Millson, Jr.
Typed or printed name of certifier

APPEAL BRIEF TRANSMITTAL

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

Appellant's revised appeal brief, in triplicate, is transmitted herewith in accordance with 37 CFR 1.192 and the Patent Office communication dated 11/30/2005 (copy also enclosed).

Respectfully submitted,

Henry E. Millson, Jr.

Henry E. Millson, Jr.
Reg. No. 18,980
Attorney for Appellant
phone and fax (928) 445-2453

675 Golden Hawk Drive
Prescott, Arizona 86301

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/053,299 | 01/17/2002 | Michael A. Zasloff | MZ 100 | 5008 |

7590 11/30/2005

HENRY E. MILLSON JR.
675 GOLDEN HAWK DRIVE
PRESCOTT, AZ 86301

| EXAMINER | |
|---|---|
| SHEIKH, HUMERA N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Notification of Non-Compliant Appeal Brief (37 CFR 41.37) | Application No. 10/053,299 | Applicant(s) ZASLOFF ET AL. | |
|---|---|---|---|
| | Examiner Humera N. Sheikh | Art Unit 1615 | |

*--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

The Appeal Brief filed on *08 September 2005* is defective for failure to comply with one or more provisions of 37 CFR 41.37.

To avoid dismissal of the appeal, applicant must file anamended brief or other appropriate correction (see MPEP 1205.03) within **ONE MONTH or THIRTY DAYS** from the mailing date of this Notification, whichever is longer. **EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136.**

1. ☒ The brief does not contain the items required under 37 CFR 41.37(c), or the items are not under the proper heading or in the proper order.

2. ☐ The brief does not contain a statement of the status of all claims, (e.g., rejected, allowed, withdrawn, objected to, canceled), or does not identify the appealed claims (37 CFR 41.37(c)(1)(iii)).

3. ☐ At least one amendment has been filed subsequent to the final rejection, and the brief does not contain a statement of the status of each such amendment (37 CFR 41.37(c)(1)(iv)).

4. ☐ (a) The brief does not contain a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number and to the drawings, if any, by reference characters; and/or (b) the brief fails to: (1) identify, for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function under 35 U.S.C. 112, sixth paragraph, and/or (2) set forth the structure, material, or acts described in the specification as corresponding to each claimed function with reference to the specification by page and line number, and to the drawings, if any, by reference characters (37 CFR 41.37(c)(1)(v)).

5. ☐ The brief does not contain a concise statement of each ground of rejection presented for review (37 CFR 41.37(c)(1)(vi))

6. ☐ The brief does not present an argument under a separate heading for each ground of rejection on appeal (37 CFR 41.37(c)(1)(vii)).

7. ☐ The brief does not contain a correct copy of the appealed claims as an appendix thereto (37 CFR 41.37(c)(1)(viii)).

8. ☐ The brief does not contain copies of the evidence submitted under 37 CFR 1.130, 1.131, or 1.132 or of any other evidence entered by the examiner **and relied upon by appellant in the appeal**, along with a statement setting forth where in the record that evidence was entered by the examiner, as an appendix thereto (37 CFR 41.37(c)(1)(ix)).

9. ☐ The brief does not contain copies of the decisions rendered by a court or the Board in the proceeding identified in the Related Appeals and Interferences section of the brief as an appendix thereto (37 CFR 41.37(c)(1)(x)).

10. ☒ Other (including any explanation in support of the above items):

*See attached.*

NOTIFICATION OF NON-COMPLIANCE WITH THE REQUIREMENTS OF 37 CFR 41.37(c).

The brief does not contain the items of the brief required by 37 CFR 41.37(c)(1) under the appropriate headings and/or in the order indicated.

A review of the application reveals that the following sections are missing from the Appeal Brief filed:

(1) "Evidence Appendix", as set forth in 37 CFR § 41.37(c)(1)(ix); and

(2) "Related Proceedings Appendix", as set forth in 37 CFR § 41.37(c)(1)(ix).

Accordingly, the Appeal Brief filed 09/08/2005 does not comply with the new rules under 37 CFR § 41.37(c). It is required that a supplemental Appeal Brief be submitted that is in compliance with 37 CFR § 41.37(c). For more information on the Boards' new rules, please see the web page entitled, "More information on the Rules of Practice Before the BPAI," Final Rule at:

http://www.uspto.gov/web/offices/dcom/bpai/fr2004/moreinfo.html

**Correspondence**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*H. N. Sheikh* H.N.S.

Patent Examiner

Art Unit 1615

November 22, 2005

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

PATENT
Docket MZ 100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re: Application of: MICHAEL A. ZASLOFF

Serial No. 10/053,299 Examiner: Sheikh, Humera, N.
Filed: 01/17/2002 Art Unit: 1615
Title: METHODS AND COMPOSITIONS FOR BLOCKING MICROBIAL ADHERENCE TO EUKARYOTIC CELLS

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Henry E. Millson, Jr. 12/17/2005
Signature of certifier Date

Henry E. Millson, Jr.
Typed or printed name of certifier

**BRIEF ON APPEAL UNDER 37 C.F.R.§ 1.192**

Commissioner for Patents
P.O.Box 1450
Alexandria, Virginia 22313-1450

Sir:

**REAL PARTY IN INTEREST**

The real party interest is Innate Immunity Incorporated, a Delaware Corporation having a place of business at 311 Sumneytown Pike, Suite 2F, North Wales, Pa. 19454-2533.

## RELATED APPEALS AND INTERFERENCES

An appeal brief was submitted in this application on October 26, 2004. In view of the appeal brief the Examiner reopened prosecution on 02/17/2005.

## STATUS OF CLAIMS

The claims in the application are claims 1-16, 18, 25, 31, 32, 34 and 41-44. The claims on appeal are all of the above claims.

The claims on appeal have been rejected under 35 U.S.C.112, first paragraph. Claims 1-6, 8-16, 18, 25 and 41-44 have been rejected under 35. U.S.C. 103(a) as being unpatentable over the Pedersen patent (6,607,711 B2). Claims 1-6, 8-13, 18, 25, 31, 32, 34 and 41-44 have been rejected under 35 U.S.C. 103(a) as being unpatentable over the Zeng patent (U.S. 6,770,306 B1).

## STATUS OF AMENDMENTS

No amendments to the claims have been proposed following the Final Rejection dated 06/03/05. Accordingly, the claims on appeal are the above claims as set forth in the APPENDIX.

## SUMMARY OF THE INVENTION

The present invention relates to methods for blocking the adherence of microorganisms to epithelial cells and other eukaryotic cells by applying isoleucine to the surface of the cells, i.e. this invention relates to a method for preventing or treating microbial infections by the application or administration of a composition containing isoleucine.

The invention also relates to compositions containing at least one isoleucine compound for applying to the above cell surfaces.

## SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1:

This claim relates to blocking microbial adherence to cell surfaces by applying to said surfaces a composition consisting essentially of an amino acid component selected from isoleucine isomers and active analogs in a microbial blocking quantity. See e.g. page 2, line 12-page 3, line 3 of the specification.

Dependent claims 2-4 set forth microbial blocking quantities. See page 2, lines 16-19.

Dependent claim 5 relates to man as the mammal. See e.g. page 4, line 13.

Dependent claim 6 relates to epithelial surfaces that can be treated with the composition of claim 1. See e.g. page 3, lines 8-13; page 7, lines 4-7; and page 4 lines 6-11.

Dependent claim 7 relates to two particular isomers of isoleucine. See page 2, lines 1 and 2.

Dependent claim 8 relates to various forms of the composition of claim 1. See e.g. page 9, lines 10-12 and page 10, line 23 – page 11, line 2.

Dependent claim 9 relates to applying directly to the epithelial surface. See e.g. page 1, line 28 – page 2, line 4 and claim 9 is an original claim.

Dependent claim 10 relates to the method of claim 1 using an aqueous composition Containing a range of amino acid component. Claim 10 is an original claim.

Claim 11:

This independent claim relates to a composition containing a range of an amino acid component selected from isoleucine isomers and active analogs, and at least one of additional named pharmacologically active substances. See page 7, line 8- page 8, line 14.

Dependent claims 12 and 13 set forth ranges for the amino acid component. See page 7, lines 14-15.

Dependent claims 14-16 relate to dental care products. See e.g. page 7, lines 16-18; and Page 9, lines 7-22.

Claim 18 relates to a toothpaste or gel containing isoleucine isomers and active analogs. See e.g. page 9, lines 7-22.

Dependent claims 25 and 31 relate to specific component B) substances of claim 11.

Dependent claim 32 relates to a wound ointment or cream. See e.g. page 12, lines 16-22.

Dependent claim 34 relates to a skin ointment or cream. See e.g. page 12, lines 13-19.

Dependent claim 41 relates to specific epithelial surfaces. See claim 6 above.

Dependent claim 42 relates to the quantity of amino acid component used in method Claim1. See e.g. page 8, lines 19 and 20 for upper end of range and page 7, line 15 for The lower end of the range.

Dependent claims 43 and 44 relate to microbial infections and bacterial infections. See e.g. page 1, line 28- page 2, line 2; page 4, line 22; page 5, line 8; and page 10, lines 1-18.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The claims on appeal have been rejected under 35 U.S.C. 103(a) as being unpatentable over the Pedersen patent (6,607,711 B2). Claims 1-6, 8-13, 18, 25, 31, 32, 34 and 41-44 have been rejected under 35 U.S.C. 103(a) as being unpatentable over the Zeng patent (U.S. 6,770,306 B1).

**ISSUES**

1. Do the claims on appeal comply with the requirements of 35 U.S.C 112, first paragraph?
2. Are the claims on appeal obvious per se over the teachings of the Pedersen reference?
3. If the Board finds the answer to issue no. 1 in the affirmative, has Appellant successfully rebutted any such presumption of obviousness?
4. Are the claims on appeal obvious per se over the teachings of the Zeng reference?
5. If the Board finds the answer to issue no. 1 in the affirmative, has Appellant successfully rebutted any such presumption of obviousness?

## GROUPING OF THE CLAIMS

The claims do not all stand or fall together for the following reasons:

1. Independent claims 1, 11, 18 and 32 each relate to different subject matter, e.g. claim 1 is a method claim; claim 11 relates to pharmacologically acceptable compositions; claim 18 relates to a toothpaste or gel; and claim 32 relates to a wound ointment or cream.
2. The claims dependent on the above independent claims that are also rejected contain additional limitations that define over the cited prior art.
3. Not all of the claims on appeal have been rejected over the Pedersen patent.
4. Not all of the claims on appeal have been rejected over the Zeng patent, and some of the claims rejected are different from those rejected over the Pedersen patent.

## ARGUMENT

Re Issue No. 1

Claims 1-16, 18, 25, 31, 32, 34 and 41-44 have been rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The Examiner contends that the claims contain subject matter which is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

The isoleucine stereoisomers and active analogs thereof, used in the practice of the invention are set forth in the paragraph bridging pages 2 and 3.

The microbial blocking quantities that can be used to obtain this effect are set forth in lines 16-19 on page 2, reproduced below:

"The microbial blocking quantity will vary depending on the isoleucine compound selected. In general, however, a quantity of from 0.1 ug/cm$^2$ to 1 gm/cm$^2$ of eukaryotic cell surface is effective, preferably from 3 ug/cm$^2$ to 100 ug/cm$^2$, and more preferably from 10 ug/cm$^2$ to 100 ug/cm$^2$."

Any physician using isoleucine can readily determine the dosage quantity needed to obtain the above microbial blocking quantities. Moreover, as with all medications, titration of dosage to obtain an effective quantity for a particular patient and condition treated is standard medical practice.

In addition, on page 7, first paragraph, reproduced below, a readily implemented method for determining an effective dose of isoleucine is set forth in clear and easily understood language directed to those skilled in this art.

"The invention also comprises a method of determining an effective dose of isoleucine comprising measuring the numbers and types of microbes contained in an epithelially lined compartment or contained in a sample taken from such a compartment, and adjusting the quantity of isoleucine accordingly. The methods of treatment described above pertain to, but are not limited to, the oral cavity and its surfaces, the entire

respiratory tract and its surfaces, the entire gastrointestinal tract and ts surfaces, the entire urogenitary tract and its surfaces and the skin."

Furthermore, dosage forms for administration of isoleucine are set forth throughout the specification; see e.g. pages 7-15, including the use of isoleucine as the only pharmacologically active component (page 8, lines 19 and 20).

The operating Examples in pages 15-20 show the use and effectiveness of the present invention for various conditions. See Examples 1-4 for the effectiveness of the present invention with respect to various types of microbes for various conditions, even where the nature of the infectious agent was unknown. See Example 2 (infectious diarrhea) and Example 3 (irritable bowel syndrome). The dosages used are set forth in all four Examples. See Example 1 page 15, lines 16-20, reproduced below:

"Isoleucine was applied by application of powder on the fingertip to the outer and inner gum margins of the upper and lower jaws. The entirety of gingival surface was covered manually, twice daily. The AM application was performed following breakfast, immediately after brushing. The PM application was conducted prior to retiring for sleep."

See Example 2, page 18, lines 11-15, reproduced below:

"Six days after ingestion of the diarrheal agent, one individual (MZ) was begun on oral isoleucine (ILE) therapy, while the other two continued on restricted diets. ILE (#E-2025 Bachem, lot 511191) was dissolved in distilled water to 0.001% One glass of

ILE solution (about 250 ml) was consumed every several hours. A total of about 4 liters was consumed over 3 ½ days."

See Example 3, page 19, lines 19-20, reproduced below:

"Each individual was given isoleucine, 1 tsp, twice a day, each dose mixed in ½ cup of yogurt."

See Example 4, page 20, lines 14-20, reproduced below:

"Isoleucine was self-administered as a powder locally within the vaginal cavity digitally, twice a day. Within 2 days symptoms of vaginosis disappeared. Isoleucine therapy was continued for several days following termination of menstrual discharge, and then stopped. The individual remained symptom free following cessation of isoleucine administration. Isoleucine was again administered during the following months, cycled as described initially. Based on the symptoms and signs, the chronic vaginosis appears to have been effectively cured."

Hence, it is contended that the enablement requirement of section 112 has been fully met.

The Examiner's consideration of factors to be considered on pages 2-4 of the Final Rejection include the following:

> (2) The state of the prior art. The Examiner's statement of the teachings of the prior art is not believed to be correct since in the Pedersen patent it is a complex metal chelate wherein the metal ion component of the chelate

is the effective agent (see col. 8 lines 3-9), and in the Zeng patent the amino acids are used as neutralizing agents for highly acidic vaginas. The above will be discussed in detail with respect to the prior art rejections.

(3) Since the Examiner agrees that the relative skill of those in the art is high, those skilled in the art would have no problems with enablement for the reasons discussed above.

(4) The Examiner's statement that the predictability of the art is high and the reasons given therefor are again not believed to be correct (see item (2) discussion above) and will be discussed in detail with respect to the section 103 rejections.

(5) The claims, except for claim 44, are broad with respect to blocking microbial adherence to eukarytic cells, since blocking the cell surfaces will prevent any microbe from attaching to the cells, and therefore the invention is broad with respect to microbe blocking. Moreover, the Examples show the effectiveness of the present method with respect to various types of bacteria.

It is true that most of the claims permit the blockage of any microbe, since this is the invention. Blocking cell surfaces will be effective in preventing or minimizing the attachment thereto of microbes generally. Moreover, the specification specifically refers to the treatment

of bacterial infections (see page 10, lines 4), yeast infections (page 10, lines 4 and 5), and viruses (common cold) (page 13, lines 6-8). See also the Examples, where gingival infections (Example 1), infectious diarrheas (Example 2), irritable bowel syndrome (Example 3), and bacterial vaginosis (Example 4) were effectively treated with isoleucine. Hence, the effectiveness of isoleucine for the treatment of various microbes has been fully disclosed in the specification.

With respect to item (6) on page 4 of the Final Rejection, the Examiner questions how isoleucine can treat or prevent an entire group of microbes. The treatment or prevention of an entire group of microbes results from the blockage of cell surfaces with isoleucine which minimizes or prevents the adhesion thereto by microbes (see e.g. page 5, lines 1-3 of the instant specification ).

Concerning the term "preventing" on page 5, line 8 of the present specification, this term does not imply a cure. First of all, the term "cure" refers to the bringing about of the recovery from a disease. The term "prevention" refers to keeping a disease from happening. Also, there is no provision in the specification suggesting or stating that the method of the invention provides a cure (except in Example 4). See e.g. page, 6, lines 19 and 20 where it is stated that "the method of the invention will either prevent adhesion of microbes to eukaryotic cells or will at least reduce

their abundance." See also Example 3 where isoleucine was effective in relieving irritable bowel syndrome, a condition for which the etiology is unknown. Each individual was maintained on isoleucine for 1 month with a consistent response. Yet, when isoleucine was withdrawn, former symptoms reappeared. Hence, for this condition, the individuals were not "cured".

Appellant is not claiming a cure, even though it appeared that a cure was obtained in Example 4 against chronic vaginosis.

With respect to Examiner's contention that " the specification provides no guidance on how the treatment or prevention of microbes can be provided through the use of one single amino acid, isoleucine", the Board's attention is respectfully directed to such teachings in the specification. See pages 2-20 for teachings too extensive to reproduce in this brief.

Concerning item (7) on page 4 of the action, it is not understood what the Examiner means by the examples being too limited. The teachings in the specification are broad. If the Examiner is referring to a necessity for extensive clinical trials, such as those required for an NDA, there is no such requirement in patent law or practice.

The working examples, although limited in patient numbers, showed that in every case the treatment was effective over a wide range of

conditions. These examples are of course not based on extensive clinical trials with large numbers of subjects, but this does not take away from the fact that in every case and every condition tested, the present method was effective. As stated above, Appellant, is not required by any law or practice to present extensive clinical studies such as those required for a New Drug Application.

The Examiner further contends that the examples are distinct from the scope of the claims. There is of course no requirement that the claims must be limited to the scope of the operating examples. Operating examples are in fact not even required in order to obtain claims to an invention.

In item (8) on page 4 of the Final Rejection, the Examiner contends that "undue" and painstaking experimentation would be required to determine which particular microbes would be positively affected by isoleucine. It is not agreed that undue or painstaking experimentation would be required to determine effectiveness for a particular microbe.

The microbial blocking quantities that can be used to obtain the desired result are set forth in lines 16-19 on page 2. Any physician using isoleucine can readily determine the dosage quantity needed to obtain the above microbial blocking quantities.

In addition, on page 7, first paragraph quoted above, a readily implemented method for determining an effective dose of isoleucine is set forth in clear and easily understood language addressed to those skilled in the art.

Furthermore, dosage forms for administration of isoleucine are set forth throughout the specification; see e.g. pages 7-15, including the use of isoleucine as the only pharmacologically active component (page 8, lines 19 and 20).

With respect to determining which particular microbes would be positively affected by the administration of isoleucine, this is readily and easily determined by using a disclosed dosage form to treat a patient having a particular microbial infection and titrating the dosage upward, if needed, until a positive effect is obtained. This is standard medical practice, employed by physicians even with well known marketed pharmaceuticals.

On page 5 of the Final rejection, the Examiner contends that:

The process steps and written description are insufficient and have not been presented in such a way as to allow one of ordinary skill in the art to understand and practice the invention. No specific formulations, specific amounts and specific procedures or administrations are set forth to allow one of ordinary skill to know how to perform a method of blocking microbial adherence to eukaryotic cells by applying an isoleucine composition."

With respect to the inability of one of ordinary skill in the art to understand and practice the invention, the Examine in item (3) on page 3 states: "The relative skill of

those in the art is high". As discussed above, the specification and operating examples are replete with clear and extensive teachings leading to both an understanding of and practicing of the invention. Appellant fails to understand the Examiner's assertions to the contrary.

Concerning specific formulations, specific amounts and specific procedures, these are given throughout the description and operating examples. See pages 2 to 20, especially page 2 lines 16-19, and page 7, lines 1-7 and 8-15.

The methods of treatment of various conditions are set forth on pages 10-15, and in the operating examples on pages 15-20.

In the "Response to Arguments" on pages 11 and 12 of the Final Rejection, the Examiner contends that with respect to the section 112 rejection, the microbial blocking quantities are not recited in the generic claims. This is respectfully submitted to be irrelevant-the section 112, first paragraph rejection refers to the "written description of the invention", and is not limited to the claims. The written description is contended to be fully enabling.

The Examiner then argues that the instant process is not enabled to demonstrate how to measure and identify specific microbes. This argument is not understood since the microbiological identification of microbes results from cultures taken from an infected patient, as well as from specific symptoms readily recognized by the medical profession.

The Examiner again refers to the claims as not "limited to the specific scopes argued by the Applicant". As stated above, enablement under the first paragraph of section 112 refers to the "written description of the invention", and not to the scope of the claims.

In the Advisory Action dated 07/18/05, the Examiner contends that Applicant's argument that "microbial blocking quantities that can be used to obtain this effect are set forth in lines 16-19 on page 2" is not persuasive since the microbial blocking quantities argued by the Applicant are not recited in the generic claims.

There is of course no requirement that the microbial blocking quantities be present in the generic claims. The generic claims recite "present in a microbial blocking quantity" (see e.g. claim 1), and the specification discloses what constitutes microbial blocking quantities as discussed above.

It is respectfully submitted that the Examiner is confusing enablement, which relates to the sufficiency of the teachings in the specification for enabling those skilled in the art to practice the invention, with arguments relating to the scope of the claims, which do not relate to enablement.

The Examiner further argues that the readily implemented method for determining an effective dose of isoleucine set forth in clear and readily understood language, "is not persuasive since the instant process is not enabled so as to demonstrate how to measure and identify specific microbes".

Methods for measuring and identifying particular microbes are of course well known to those skilled in this art, and there would be no point or benefit to include such well known methods in this application. It is respectfully submitted that enablement is present without including such well known technology.

In view of the above discussion, the Board is respectfully requested to find for Appellant for Issue No. 1, i.e. that the specification is fully enabling for the claimed invention.

Re Issue No. 2

On page 5 of the Final Rejection claims 1-6, 8-16, 18, 25, and 41-44 have been rejected under 35 U.S.C. 103(a) as being unpatentable over the Pedersen reference.

The Examiner's interpretation of the claims as permitting mixtures of amino acids is respectfully submitted to be incorrect. Claim 1 for example limits the amino acid component to an isoleucine compound; hence excluding mixtures of amino acids. The Examiner's statement that isoleucine is "preferred" is also not correct. It is the isoleucine compound that blocks microbial adherence to cell surfaces and not other amino acids, i.e. the invention relates to isoleucine isomers and analogs as the only active agent.

As noted by the Examiner, Pedersen's compositions require the use of chelates of a metal ion, in which it is the metal ion that reduces microbial growth potential to combat halitosis. See e.g. The SUMMARY OF THE INVENTION in column 3, lines 25-36, where it is stated that: It has now surprisingly been found that various metals, including

zinc provided to the oral cavity as part of a metal amino acid chelate, are capable of effectively reducing or eminating bad or unpleasant breath..."

The metal chelate is described in column 4, lines 4-11 as "The resulting molecule has two or three five-membered heterocyclic ring structures containing a metal ion attached by coordinate covalent bonds to two or more non-metals in the same molecule. Such chelates differ from traditional salts by having different physical and chemical properties such as e.g. the nature of the chemical bonds involved in forming the different chemical structures."

The two paragraphs following this quotation make it additionally clear that the chelate is not an amino acid salt.

Hence, the amino acids used to form the chelates are reaction products only and do not exist as such in the chelate. Isoleucine does not have "two or three five-membered heterocyclic ring structures", i.e. isoleucine has the following structure: $CH_3CH_2CH(CH_3)CH(NH_2)C00H$.

See also the chelate structures in the Pedersen patent set forth in column 6, lines 50-55 and column 11, lines 5-8 where the chelates are bicyclic structures. The chelates are stable compounds which however react by means of the metal ion with sulfur-containing amino acids in the oral cavity to reduce microbial growth potential (see e.g. column 8, lines 5-9).

The two paragraphs following this quotation make it additionally clear that the chelate is not an amino acid salt.

Hence, the amino acids used to form the chelates are reaction products only and do not exist as such in the chelate. Isoleucine does not have "two or three five-membered heterocyclic ring structures".

Hence, it is respectfully contended that the chelate of Pedersen is chemically unrelated to isoleucine, and functions by an entirely different mechanism, i.e. metal ion reaction with sulfur-containing amino acids in the oral cavity.

Also, as noted by the Examiner, Pedersen does not teach Appellant's claimed ranges. However, since the compounds used in the respective inventions are chemically quite dissimilar their respective ranges are respectfully submitted to be irrelevant. Moreover, since both the products and mechanisms of action are unrelated, any test of discovering "optimum or workable ranges" cannot apply here.

On page 12 of the Final Rejection, the Examiner contends that "the presence of metal ions is considered equivalent to Applicant's invention". As discussed above, the metal chelates of Pedersen are cyclic compounds with which the present invention is not in any way related, and function by an entirely different mechanism. The use of a mixture of amino acids by Pedersen to form his metal chelates are reactants, not present as such in the cyclic chelate compounds.

The rejected claims, including some of the dependent claims, contain at least the following limitations not taught or suggested by the Pedersen reference.

Claim 1-

(a) a method of blocking microbial adherence to a eukaryotic cell surface in a mammal by applying to said surface.....

(b) a pharmacologically acceptable composition consisting essentially of an amino acid component selected from the group consisting of at least one of (an isoleucine isomer and active analogs of isoleucine)...

(c) present in a microbial blocking quantity.

Pedersen discloses none of the above limitations.

Claims 2-4-

contain additional limitations relating to ranges of microbial blocking quantities.

Pedersen does not disclose such ranges.

Claim 8-

contains forms of the composition.

Pedersen does not disclose such compositions for isoleucine.

Claim 10-

(a) aqueous composition.

(b) containing 0.01-50 ug/ml of the amino acid component.

Pedersen does not disclose either of such additional limitations.

Claim 11-

(a) from about 0.001 to about 99% by weight.

(b) of an isoleucine amino acid component.

(c) at least one listed additional active substance.

Pedersen does not disclose any of the above.

Claims 12 and 13-

additional weight limitations for isoleucine amino acids.

No such disclosure by Pedersen.

Claim 18-

(a) a cell surface blocking quantity.

(b) of an isoleucine amino acid component.

(c) in a toothpaste or gel form.

No such disclosure by Pedersen.

Claim 42-

quantity of amino acid component.

Not disclosed by Pedersen.

Claim 44-

infectious agent is bacteria.

Not disclosed by Pedersen.

Since Pedersen does not disclose any of the above limitations, it is respectfully contended that the presently rejected claims are not obvious in view of the teachings in the Pedersen reference.

It is of course improper to rebuild a reference, in light of applicant's disclosure, in order for it to operate in a manner never intended or contemplated by the reference. Ex parte Garrett, POBA (1961) 132 USPQ 514. The reference, viewed by itself and not in retrospect, must suggest doing what applicant has done. In re schaffer(CCPA 1956) 108 USPQ 326; In re Skoll (CCPA 1975) 187 USPQ 481.

The Board is respectfully requested to find in favor of Appellant with respect to Issue No. 2.

Re Issue No. 3

In the event the Board finds against Appellant with respect to Issue No. 2, it is respectfully contended that any case of obviousness per se is rebutted by the following discoveries:

> In the operating Examples, in Example 1 individuals having clinically evident low grade gingivitis were treated with isoleucine powder applied to the outer and inner gum margins of the upper and lower jaws. After 7 days of treatment 80% of the cells were completely free of bacteria, while another 15% contained only 1-10 bacteria, and only 5% had a continuous lawn of bacteria. This result compares to 90% of the cells containing a contiguous lawn of bacteria prior to treatment with isoleucine.
>
> This result is surprising and unpredictable and clearly not taught or

suggested by the Pedersen reference. In particular, this result was obtained using the amino acid isoleucine (and not a metal chelate where the metal ion is the effective halitosis agent). There is no disclosure in Pedersen leading one skilled in this art to use isoleucine absent a cyclic metal chelate for treatment of a gingivitis infection, particularly since Pedersen makes it clear that the metal ion in the chelate is the effective anti-halitosis agent.

In Example 2 on pages 17-19, isoleucine was administered to treat infectious diarrhea. No medications were administered to the three patients having the infectious diarrhea.. One individual was treated with oral isoleucine, six days after ingestion of the infectious agent, while the other two continued on restricted diets. A reduction of stool frequency was noted with the isoleucine patient within 12 hours of initiation of isoleucine therapy. This reduction continued until the third day when no stools were passed. By day 4 normal stool was passed and the diarrheal episode had passed.

The two patients not treated with isoleucine experienced diarrhea for 11 days after ingestion of the infectious agent.

This is an unexpected and surprising discovery in no way taught or suggested by the Pedersen reference.

In Example 3, two women having irritable bowel syndrome (IBS) were treated with isoleucine in yogurt, where the yogurt itself had little effect on the IBS from previous experience.

Within 2 days of isoleucine administration, bloating, urgency to defecate, and gaseousness had disappeared. Both individuals described their bowel function as normal for the first time in 20 years.

The above results were unexpected and unobvious. The Pedersen patent contains no such disclosure.

In Example 4 bacterial vaginosis was effectively treated in the vaginal cavity – in 2 days symptoms of vaginosis disappeared. The individual remained symptom free following cessation of isoleucine therapy.

The above results are also unexpected and clearly not taught or suggested by Pedersen.

In view of the above, the Board is respectfully requested to find for Appellant with respect to Issue No. 3.

Re: Issue No. 4

Claims 1-13, 18, 25, 31, 32, 34 and 41-44 have been rejected under 35 U.S.C. 103(a) as being unpatentable over the Zeng reference. (U.S. 6,770,306 B1).

The Zeng reference is directed to

> "a pharmaceutical composition which is effective in reducing vaginal acidity, the inventor has conducted extensive study. Surprisingly, the inventor discovered that amino acids, salts of amino acids, oligopeptides and polypeptides can change the metabolic process of bacteria in the vagina and reduce vaginal acid production, and can be used to reduce vaginal acidity, a longer treatment was obtained compared to the treatment of directly using alkali substances. Based on his discovery and further study, the inventor completed the present invention.
>
> The invention proves a pharmaceutical composition for reducing vaginal acidity and it is characterized by containing containing one or more components defined as follows: amino acids, physiologically acceptable salts of amino acids, oligopeptides and polypeptides; optionally containing pharmaceutically acceptable alkali substances; optionally, containing anti-fungal drugs of an effective amount; and one or more pharmaceutically acceptable carriers." See column 3, lines 42-59 under the "DESCRIPTION OF THE INVENTION."

In column 4, lines 11-21, it is stated that "According to the invention, the amino acids in the said composition are formulations or combinations of many amino acids..." (underlining added), and then lists 20 amino acids that can be used to form the "many amino acids". Isoleucine is included as one of the amino acids that can be present in the many amino acid mixtures.

In column 4, lines 47-49, it is stated that "the composition containing only one or two sodium salts of amino acids can also party (partly) realize the object of the invention.", i.e. the use of only one or two sodium salts of amino acids cannot fully realize the object of the invention. This statement in effect directs one skilled in the art away from using only one or two amino acid salts in the invention. In fact, in the twenty operating Examples in columns 7-12, none of the compositions in which amino acids were used employed fewer than 8 amino acids.

With respect to the treatment of fungal vaginitis, in column 14, lines 49-54, it is stated that "..even the composition of the invention containing no anti-fungal agents can cure some of the vaginal fungal infections.." This statement evidently refers to Experimental Example 1, where a patient with a fungal infection was treated with the composition of Example 1. The composition of Example 1 employed a mixture of 9 amino acids (including isoleucine) together with yeast extract powder, which contains "abundant of amino acids, oligopeptide, and other protein hydrolytic products and vitamins" (column 14, lines 34-36). There was no determination whether or not any particular component or components of this mixture possessed antifungal activity or whether it was simply the reduction in acidity that produced the antifungal activity.

In column 7, lines 37-42, it is stated that "For the cases with typical fungal vaginitis, in particular for repeated and stubborn fungal vaginitis, the patient can be

treated with the composition of this invention containing anti-fungal agents until the symptoms are alleviated." (underlining added). Hence cases of typical fungal vaginitis require the presence of anti-fungal agents for effective treatment.

The Examiner has interpreted the present claims as permitting mixtures of amino acids, and refers to isoleucine as a preferred amino acid. As discussed above, this assumption is not accurate, since the prsent inventors have found that isoleucine, and only isoleucine and its steroisomers and active analogs, have the unexpected benefits of blocking eukaryotic cell surfaces to prevent or at least significantly decrease microbial attachment to such cell surfaces. Independent claims 1, 11, 18 and 32 limit the amino acid component to isoleucine and its analogs. Also, component B) in claim 1 excludes other amino acids as an additional pharmacologically active substance.

The Examiner on page 9 of the Final Rejection refers to overlapping amounts of isoleucine. However, the amino acids are used in Zeng's invention to treat highly acidic vaginas to increase the pH of the vagina, i.e, Zeng's amino acid mixtures are used as neutralizing agents. Whether or not any isolueicine remains in the vagina after such neutralization is unknown and amounts to unfounded speculation, especially since Zeng does not teach the use of a amino acid mixtures in excess of that needed for pH control.

Also, as noted by the Examiner, Zeng does not teach Appellant's ranges of microbial blocking quantities for cell surfaces using only isoleucine as recited in claims 2-4. The argument concerning the finding of suitable ranges is not relevant, since the use of amino acid mixtures, oligpeptides and polypeptides as neutralizing agents has nothing

to do with using only isoleucine for the blocking of cell surfaces to block microbial adherence.

The discovery of optimum or workable ranges by routine experimentation for blocking cell surfaces using only isoleucine presupposes that Zeng knew about such a concept, which clearly he did not.

With respect to the "Response to Arguments" on page 12 of the Final Rejection, the Examiner contends that "the mixtures function in a similar manner." This is not in fact correct. Zeng's mixtures of amino acids function as neutralizing agents for highly acidic vaginas, i.e. as reactants for removing acidic components from the vagina. This is not functioning in a similar meanner to the use of a single amino acid, isoleucine, to block microbial adherence to cell surfaces. As discussed above, there is moreover no reason to assume that the resulting reaction products obtained by Zeng will leave sufficient unreacted isoleucine to function as an effective blocking agent on cell surfaces, particularly since Zeng does not teach or suggest any reason for using quantities of neutralizing agents in excess of those needed to neutralize the acidic components in the highly acidic vaginas.

In the fourth paragraph on Page 12 of the Final Rejection, the Examiner rejects one of Appellant's arguments "because the mixtures function in a similar manner."

As discsussed above, Zeng's compositions containing amino acid mixtures are used to treat vaginitis resulting from highly acidic vaginas, i.e. as neutralizing agents.

This disclosure has nothing to do with the method for blocking microbial adherence to eukaryotic cell surfaces (claims 1-10 and 41-44). This is not "function in a similar manner". Zeng does not teach any method for blocking cell surfaces using an isoleucine compound.

The claims on appeal rejected over the Zeng reference contain a number of limitations not taught or suggestged by the Zeng reference, discussed below.

Claim 1:

a) a method of blocking microbial adherence to a eukaryotic cell surface.-

b) by applying to said surface ... an amino acid component selected from the group consisting of (isoleucine isomers and active analogs)..

c) present in a microbial blocking quantity.

Claims 2-4: ranges of microbial blocking quantities

Claim 11: amino acid component selected from the group consisting of (isoleucine isomers and active analogs of isoleucine)...

Claims 12-13: quantities of the isoleucine present in the composition.

Claim 18:

a) a toothpaste or gel...

b) amino acid component present in a cell surface blocking quantity...

c) which is an isoleucine isomer or active analog thereof.

Claim 31: composition in the form of a wound ointment or cream.

Claim 32:

a) wound ointment or cream...

b) cell blocking quantity...

c) of an isoleucine isomer or active analog.

Claim 34: skin ointment or cream

Claim 44: method for treatment of bacterial infection.

Hence it is respectfully contended that the claims rejected over the Zeng reference are not prima facie obvious over this reference, and the Board is accordingly requested to find for Appellant with respect to Issue No. 4.

Re: Issue No. 5

Rebuttal of any finding of prima facie obviousness is the same as that set forth for the Pedersen reference, i.e. the same as Issue No. 3.

None of the discoveries in the operating Examples are taught or suggested by Zeng with respect to the unexpected results obtained using only isoleucine as a cell surface blocking agent.

Accordingly, the Board is respectfully requested to find for Appellant with respect to Issue No. 5.

Respectfully submitted,

Henry E. Millson, Jr.

Henry E. Millson, Jr.
(Reg. No. 18,9890)
Attorney for Applicant
675 Golden Hawk Drive
Prescott, Arizona 86301
Phone and fax (928) 445-2453

## APPENDIX

## CLAIMS ON APPEAL

1. A method of blocking microbial adherence to a eukaryotic cell surface in a mammal by applying to said surface a pharmacologically acceptable composition consisting essentially of an amino acid component selected from the group consisting of at least one of the following: L(+-) isoleucine, DL-isoleucine, D(-) – allo-isoleucine, L(+)-allo-isoleucine, and active analogs of isoleucine present in a microbial blocking quantity.
2. The method of claim 1 wherein the microbial blocking quantity is in the range of from about 0.1 ug/cm$^2$ to about 1 gm/cm$^2$ of eukaryotic cell surface area.
3. The method of claim 2 wherein said quantity is from about 3 ug/cm$^2$ to about 100 ug/cm$^2$.
4. The method of claim 2 wherein said quantity is from about 10 ug/cm$^2$ to about 100 ug/cm$^2$.
5. The method of claim 1 wherein the mammal is mankind.
6. The method of claim 1 wherein the epithelial surface is one or more of the oral cavity, pharynx, GI tract, respiratory tract, genitourinary tract, skin, eye, and vaginal/cervical area.
7. The method of claim 1 wherein the composition consists of a pure powder of L(+)-isoleucine and/or DL-isoleucine.
8. The method of claim 1 wherein the composition is in the form of a dry powder, a paste, a solution, a gel, a tablet, a lozenge, or a capsule.

9. The method of claim 1 wherein the composition is directly applied to the said epithelial surface.

10. The method of claim 1 wherein the composition is in the form of a pharmacologicaly acceptable aqueous composition containing from about 0.01 ug/ml to about 50 ug/ml of said amino acid component.

11. A pharmaologically acceptable composition consisting essentiallly of:

    A) from about 0.001 to about 99% by weight of an amino acid component selected from the group consisting of at least one of the following: L(+) isoleucine, DL-isoleucine, D(-)-allo-isoleucine, L(+)-allo-isoleucine, and active analogs of isoleucine;

    B) at least one additional pharmacologically active substance selected from the group consisting of a fluoride, xylitol, an antibody, an anti-microbial agent, zinc ions, a decongestant, an anesthetic, an anti-oxidant, a vitamin, a microbial substance, a pre-biotic material, folic acid, echinacea, peppermint oil or extract, menthol, quassia, bistort, ginger, angelica, bayberry, chamomile, fish oil, or fractionated fish oil, a fatty acid, fiber, flaxseed, a plant extract, garlic or garlic extract, calcium, stannol esters, lutein, zeaxanthin, cryptoxanthin, isolflavone, an anti-inflammatory compound, an antifungal agent, and a food product; and optionally,

    C) pharmacologically acceptable carrier materials and/or excipients.\

12. The composition of claim 11 wherein component A) is present in from about 0.002 to about 50% by weight.

13. The composition of claim 11 wherein component A) is present in from about 0.1 to about 25% by weight.

14. The composition of claim 11 wherein said composition is in the form of a dental care product.

15. The composition of claim 14 wherein component B) is one or more of a fluoride, xylitol, an antibody, and an anti-microbial agent.

16. The composition of claim 14 wherein the composition is in the form of a toothpaste or a gel.

18. A toothpaste or gel comprising a eukaryotic cell surface blocking quantity of an amino acid component selected from the group consisting of at least one of the following: L(+) isoleucine, DL-isoleucine, D(-)-allo-isoleucine, L(+)-allo-isoleucine, and active analogs of isoleucine.

25. The composition of claim 11 wherein component B) is an antifungal and/or antimicrobial substance.

31. The composition of claim 11 wherein the composition is in the form of a wound ointment or cream and component B) is one or more of an antimicrobial substance and an anesthetic.

32. A wound ointment or cream comprising a eukaryotic cell surface blocking quantity of a compound consisting essentially of an amino acid component selected from the group consisting essentially of at least one of the following: L(+) isoleucine, DL-isoleucine, D(-)-allo-isoleucine, L(+)-allo-isoleucine, and active analogs of isoleucine.

34. The composition of claim 11 wherein the composition is in the form of a skin

ointment or cream.

41. The method of claim 1 wherein the epithelial surface is one or more of the oral cavity, GI tract, respiratory tract, genitourinary tract, skin, and eye.

42. The method of claim 1 wherein the amino acid component is present in from about 0.1 to 100% by weight of the composition.

43. The method of claim 1 wherein the method is used to treat an infection caused by microbes.

44. The method of claim 43 wherein the microbes are bacteria.

## EVIDENCE APPENDIX

There was no evidence submitted by appellant pursuant to §§ 1.130,1.131, or 1.132 during the prosecution of this application, or relied upon by appellant in this appeal.

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## RELATED PROCEEDINGS APPENDIX

There are no decisions rendered by a court or the Board in any proceedings identified pursuant to 37 CFR §41.37 (c) (i) (ii).